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<p>(21) International Application Number: PCT/US97/18956</p> <p>(22) International Filing Date: 23 October 1997 (23.10.97)</p> <p>(30) Priority Data: 60/030,424 24 October 1996 (24.10.96) US</p> <p>(71) Applicant: ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).</p> <p>(72) Inventors: LEE, Eun, Soo; 108 Danbury Lane, Redwood City, CA 94061 (US). YUM, Su, Il; 1021 Runnymede Court, Los Altos, CA 94061 (US).</p> <p>(74) Agents: RAFA, Michael, J. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p>
<p>(54) Title: PERMEATION ENHANCERS FOR TRANSDERMAL DRUG DELIVERY COMPOSITIONS, DEVICES, AND METHODS</p> <div data-bbox="365 1155 1144 1386" data-label="Image"> </div> <p>(57) Abstract</p> <p>The present invention is directed to the transdermal administration of at least one drug together with a suitable amount of a permeation enhancer comprising monoalkyl ethers of polyethyleneglycol and their alkyl or aryl carboxylic acid esters and carboxymethyl ethers. The invention includes a transdermal drug delivery device comprising a matrix adapted to be placed in drug-and-permeation enhancer-transmitting relation with a skin site. The matrix contains sufficient amounts of the permeation enhancer and drug, in combination, to continuously administer drug to the systemic circulation of a patient at a therapeutically effective rate. The invention is also directed to compositions and methods for transdermal administration of at least one drug together with a permeation enhancer of this invention, alone or in combination with other enhancers.</p>		

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1 PERMEATION ENHANCERS FOR TRANSDERMAL
2 DRUG DELIVERY COMPOSITIONS, DEVICES, AND METHODS

3
4 FIELD OF THE INVENTION

5
6 This invention relates to the transdermal delivery of drugs and more
7 particularly to permeation enhancers for compositions, devices, and methods
8 for enhancing the percutaneous absorption of drugs when administered to a
9 body surface or membrane. The permeation enhancers of this invention
10 comprise monoalkyl ethers of polyethyleneglycol and their alkyl or aryl
11 carboxylic acid esters and carboxymethyl ethers. The permeation enhancers
12 of this invention are used either alone or in combination with other permeation
13 enhancers.

14
15 DESCRIPTION OF TERMS

16
17 As used herein, the term "drug" is to be construed in its broadest
18 sense to mean any material which is intended to produce some biological,
19 beneficial, therapeutic, or other intended effect, such as permeation
20 enhancement, for example, on the organism to which it is applied.

21 As used herein, the term "transdermal" refers to the use of skin,
22 mucosa, and/or other body surfaces as a portal for the administration of
23 drugs by topical application of the drug thereto.

24 As used herein, the term "therapeutically effective" amount or rate
25 refers to the amount or rate of drug needed to effect the desired therapeutic
26 result.

27 As used herein, the phrase "sustained time period" intends at least
28 about 12 hours and will typically intend a period in the range of about one to
29 about seven days.

1 As used herein, the term "individual" intends a living mammal and
2 includes, without limitation, humans and other primates, livestock and sports
3 animals such as cattle, pigs and horses, and pets such as cats and dogs.

4 As used herein, the phrase "predetermined area of skin" intends a
5 defined area of intact unbroken skin or mucosal tissue. That area will usually
6 be in the range of about 5 cm² to about 100 cm².

7 As used herein, the term "permeation enhancer" intends an agent or a
8 mixture of agents which, alone or in combination, acts to increase the
9 permeability of the skin to a drug.

10 As used herein, the term "permeation enhancement" intends an
11 increase in the permeability of skin to a drug in the presence of a permeation
12 enhancer as compared to permeability of skin to the drug in the absence of a
13 permeation enhancer.

14 As used herein, the term "permeation-enhancing" intends an amount or
15 rate of a permeation enhancer which provides permeation enhancement
16 throughout a substantial portion of the administration period.

17

18 BACKGROUND OF THE INVENTION

19

20 The transdermal route of parenteral delivery of drugs provides many
21 advantages, and transdermal systems for delivering a wide variety of drugs
22 are described in U.S. Pat. Nos. 3,598,122; 3,598,123; 3,731,683; 3,797,494;
23 4,286,592; 4,314,557; 4,379,454; 4,435,180; 4,559,222; 4,568,343; method
24 4,573,999; 4,588,580; 4,645,502; 4,704,282; 4,816,258; 4,849,226;
25 4,908,027; 4,943,435; 5,004,610; 5,314,694; and 5,411,740. In many cases,
26 drugs which would appear to be ideal candidates for transdermal delivery are
27 found to have such low permeability through intact skin that they cannot be
28 delivered in therapeutically effective amounts from reasonably sized devices.

29 In an effort to increase skin permeability so that drugs can be delivered
30 in therapeutically effective amounts, it has been proposed to pretreat the skin
31 with various chemicals or to concurrently deliver the drug in the presence of

1 a permeation enhancer. Various materials have been suggested for this,
2 as described in U.S. Patent Nos. 3,472,931; 3,527,864; 3,896,238;
3 3,903,256; 3,952,099; 4,046,886; 4,130,643; 4,130,667; 4,299,826;
4 4,335,115; 4,343,798; 4,379,454; 4,405,616; 4,568,343; 4,746,515;
5 4,764,379; 4,788,062; 4,820,720; 4,863,738; 4,863,970; 4,865,848;
6 4,900,555; 4,940,586; 4,973,468; 5,053,227; 5,059,426; 5,378,730;
7 WO 95/09006; and British Pat. No. 1,011,949. Williams et al. "Skin
8 Absorption Enhancers" Critical Review in Therapeutic Drug Carrier
9 Systems, pp. 305-353 (1992) and Santus et al. "Transdermal Enhancer
10 Patent Literature", Journal of Controlled Release, pp. 1-20 (1993) also
11 provide a recent review of transdermal permeation enhancers.

12 To be considered useful, a permeation enhancer should have the
13 ability to enhance the permeability of the skin for at least one and preferably
14 a significant number of drugs. More importantly, it should be able to enhance
15 the skin permeability such that the drug delivery rate from a reasonably sized
16 system (preferably 5 - 60cm²) is at therapeutically effective levels.
17 Additionally, the enhancer when applied to the skin surface, should be non-
18 toxic, non-irritating on prolonged exposure and under occlusion, and non-
19 sensitizing on repeated exposure. Preferably, it should be odorless,
20 physiologically inactive, and capable of delivering drugs without producing
21 burning or tingling sensations.

22 In addition to these permeation enhancer-skin interaction
23 considerations, a permeation enhancer must also be evaluated with respect
24 to possible interactions within the transdermal system itself. For example,
25 the permeation enhancer must be compatible with the drug to be delivered,
26 the adhesive, and the polymer matrix in which the drug is dispersed. The
27 permeation enhancer should also be selected so as to ensure a suitable
28 balance among tack, adhesion, and cohesive strength of the adhesive.

SUMMARY OF THE INVENTION

According to the present invention, it has been discovered that monoalkyl ethers of polyethyleneglycol and their alkyl or aryl carboxylic acid esters and carboxymethyl ethers, either alone or in combination with other permeation enhancers, enhance the permeability of the skin to transport of drugs therethrough. In addition, the combined effect of a permeation enhancer according to this invention with other permeation enhancers known in the art such as monoglycerides of fatty acids and ethanol provides a surprising, i.e. more than additive, increase in the transdermal flux of drug. The invention provides novel compositions for use with transdermal drug delivery devices and methods for effectively administering drugs and greatly increasing the drug permeability through the skin while reducing the lag time between application of the drug to the skin and attainment of the desired therapeutic effect.

Therefore, it is an object of the present invention is to provide improved drug delivery by means of transdermal systems and compositions.

A further object is to increase the transport of drugs across the skin following application of a transdermal therapeutic system.

Another object is to eliminate the lag time between the application of a transdermal therapeutic system and attainment of the desired therapeutic flux level.

Accordingly, the present invention provides compositions and devices for transdermal administration of at least one drug to the systemic circulation of a patient, at a therapeutically effective rate, by permeation through a body surface or membrane, comprising at least one drug and a permeation-enhancing amount of a permeation enhancer selected from monoalkyl ethers of polyethyleneglycol and their alkyl or aryl carboxylic acid esters and carboxymethyl ethers, either alone or in combination with other permeation enhancers. The invention further provides a method for the transdermal

1 coadministration of a drug at a therapeutically effective rate together with a
2 skin permeation-enhancing amount of the permeation enhancer.

3 The system of the invention is preferably a transdermal drug delivery
4 device comprising a matrix adapted to be placed in drug- and permeation
5 enhancer-transmitting relation with a body surface or membrane such as the
6 skin or mucosa. The system must be of a reasonable size useful for the
7 application of the drug and the enhancer to a human body.

8

9 BRIEF DESCRIPTION OF THE DRAWINGS

10

11 FIG. 1 is a cross-sectional view of one embodiment of a transdermal
12 therapeutic drug delivery device which may be used in accordance with the
13 present invention.

14 FIG. 2 is a cross-sectional view of another embodiment of a
15 transdermal therapeutic drug delivery device which may be used in
16 accordance with the present invention.

17 FIG. 3 is a cross-sectional view of yet another embodiment of a
18 transdermal therapeutic drug delivery device which may be used in
19 accordance with this invention.

20 FIG. 4 is a cross-sectional view of yet another embodiment of a
21 transdermal therapeutic drug delivery device which may be used in
22 accordance with this invention.

23 FIG. 5 is a plot showing the cumulative release of testosterone through
24 human epidermis at 35° C, in vitro, from donor solutions containing varying
25 amounts of laureth-4, alone or in combination with ethanol.

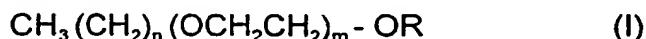
26 FIG. 6 is a plot showing the flux of oxybutynin through human
27 epidermis at 35° C, in vitro, from an EVA matrix system containing laureth-2
28 or lauryl lactate, each in combination with GML.

29 FIGS. 7-18 are plots of the flux of various drugs through human
30 epidermis at 35° C, in vitro, showing the increased skin permeability obtained
31 from various permeation-enhancing mixtures of this invention.

DETAILED DESCRIPTION OF THE INVENTION

According to this invention, it has been discovered that monoalkyl ethers of polyethyleneglycol and their alkyl or aryl carboxylic acid esters and carboxymethyl ethers, either alone or in combination with other permeation enhancers, substantially increase the permeability of a body surface or membrane to transport of at least one drug therethrough. Additionally, the combination of the permeation enhancers according to this invention with other permeation enhancers known in the art, such as ethanol and monoglycerides, provides a synergistic effect on the transdermal flux of a drug. The permeation enhancers of this invention can be used to effectively enhance the permeability of drugs through body surfaces or membranes in general and particularly through the skin.

The monoalkyl ethers of polyethyleneglycol and their alkyl or aryl carboxylic acid esters and carboxymethyl ethers of this invention are represented by the following formula:



wherein $n = 3-19$; $m = 1-20$; and $R = \text{i)H}$; $\text{ii) CH}_2\text{COOH}$; or iii) OC-R'

where R' is an alkyl or aryl group comprising 1-16 carbons. Preferably, the permeation enhancer is selected from polyethyleneglycol monolauryl ethers and their alkyl or aryl carboxylic acid esters and carboxymethyl ethers.

Preferred enhancers according to this invention include diethylene glycol monododecyl ether, tetraethylene glycol monododecyl ether, diethylene glycol monododecyl ether acetate, diethylene glycol monododecyl ether benzoate, triethylene glycol monododecyl ether carboxylic acid, and polyethylene glycol monododecyl ether carboxylic acid.

The permeation enhancers according to this invention may be used alone or in combination with other permeation enhancers known in the art, including, but not limited to monoglycerides or mixtures of monoglycerides of fatty acids such as glycerol monolaurate, glycerol monooleate, and glycerol monolinoleate, lauramide diethanolamine, lower C_{1-4} alcohols, alkyl laurates

1 such as methyl laurate, acyl lactylates, dodecyl acetate, and C₁₀ - C₂₀ fatty
2 acid esters including lactic acid esters such as lauryl lactate, myristyl lactate,
3 and cetyl lactate. A preferred embodiment is directed to the use of a
4 permeation enhancer according to Formula I in combination with ethanol
5 or a monoglyceride of a fatty acid, such as glycerol monolaurate or glycerol
6 monooleate.

7 The examples that follow demonstrate the utility of the permeation
8 enhancers of this invention for several dissimilar drugs. It is believed that this
9 invention has utility in connection with the delivery of drugs within the broad
10 class normally delivered through body surfaces and membranes, including
11 skin. In general, this includes therapeutic agents in all of the major areas,
12 including, but not limited to, ACE inhibitors, adenoypophoseal hormones,
13 adrenergic neuron blocking agents, adrenocortical steroids, inhibitors of the
14 biosynthesis of adrenocortical steroids, alpha-adrenergic agonists, alpha-
15 adrenergic antagonists, selective alpha-two-adrenergic agonists, analgesics,
16 antipyretics and anti-inflammatory agents, androgens, local and general
17 anesthetics, antiaddictive agents, antiandrogens, antiarrhythmic agents,
18 antiasthmatic agents, anticholinergic agents, anticholinesterase agents,
19 anticoagulants, antidiabetic agents, antidiarrheal agents, antidiuretic,
20 antiemetic and prokinetic agents, antiepileptic agents, antiestrogens,
21 antifungal agents, antihypertensive agents, antimicrobial agents, antimigraine
22 agents, antimuscarinic agents, antineoplastic agents, antiparasitic agents,
23 antiparkinson's agents, antiplatelet agents, antiprogestins, antithyroid agents,
24 antitussives, antiviral agents, atypical antidepressants,
25 azaspirodecanediones, barbituates, benzodiazepines, benzothiadiazides,
26 beta-adrenergic agonists, beta-adrenergic antagonists, selective beta-one-
27 adrenergic antagonists, selective beta-two-adrenergic agonists, bile salts,
28 agents affecting volume and composition of body fluids, butyrophenones,
29 agents affecting calcification, calcium channel blockers, cardiovascular drugs,
30 catecholamines and sympathomimetic drugs, cholinergic agonists,
31 cholinesterase reactivators, dermatological agents, diphenylbutylpiperidines,

1 diuretics, ergot alkaloids, estrogens, ganglionic blocking agents, ganglionic
2 stimulating agents, hydantoins, agents for control of gastric acidity and
3 treatment of peptic ulcers, hematopoietic agents, histamines, histamine
4 antagonists, 5-hydroxytryptamine antagonists, drugs for the treatment of
5 hyperlipoproteinemia, hypnotics and sedatives, immunosuppressive agents,
6 laxatives, methylxanthines, monoamine oxidase inhibitors, neuromuscular
7 blocking agents, organic nitrates, opioid analgesics and antagonists,
8 pancreatic enzymes, phenothiazines, progestins, prostaglandins, agents for
9 the treatment of psychiatric disorders, retinoids, sodium channel blockers,
10 agents for spasticity and acute muscle spasms, succinimides, thioxanthines,
11 thrombolytic agents, thyroid agents, tricyclic antidepressants, inhibitors of
12 tubular transport of organic compounds, drugs affecting uterine motility,
13 vasodilators, vitamins and the like, alone or in combination.

14 Administration of the drug according to the invention comprises
15 administering at least one drug at a therapeutically effective rate to an area of
16 a body surface or membrane and simultaneously administering a permeation
17 enhancer of this invention to the area of the body surface or membrane at a
18 rate sufficient to substantially increase the permeability of the area to the drug
19 formulation.

20 According to the invention, the permeation enhancer and the drug to
21 be delivered are placed in drug- and permeation enhancer-transmitting
22 relationship to the appropriate body surface, preferably in a carrier therefor,
23 and maintained in place for the desired period of time. The drug and
24 permeation enhancer are typically dispersed within a physicochemically and
25 biologically compatible matrix or carrier which may be applied directly to the
26 body surface or skin as an ointment, gel, cream, suppository or sublingual or
27 buccal tablet, for example, but are more preferably administered from a
28 transdermal therapeutic delivery device as more fully described below.
29 When used in the form of a liquid, ointment, cream, or gel applied directly
30 to the skin, it is preferable, although not required, to occlude the site of
31 administration. Such compositions can also contain other permeation

1 enhancers, stabilizers, dyes, diluents, pigments, vehicles, inert fillers,
2 excipients, gelling agents, vasoconstrictors, and other components of typical
3 compositions as are known to the art.

4 The permeation enhancer of this invention has a permeation-
5 enhancing effect on the transport of drugs through body surface tissues
6 generally, in addition to the skin. However, because skin is one of the most
7 effective body barriers to the permeation of foreign substances, the effect of
8 the permeation enhancer composition on skin permeation makes it extremely
9 useful in transdermal delivery. The following description of embodiments of
10 the invention is therefore directed primarily to improving systemic delivery of
11 these drugs by permeation through the skin.

12 The permeation enhancer is dispersed throughout the matrix or carrier,
13 preferably at a concentration sufficient to provide permeation-enhancing
14 amounts of enhancer in the reservoir throughout the anticipated
15 administration period. Where there is an additional, separate permeation
16 enhancer matrix layer as well, as in FIG. 2, the permeation enhancer normally
17 is present in the separate reservoir in excess of saturation.

18 One embodiment of a transdermal delivery device of the present
19 invention is illustrated in FIG. 1. In FIG. 1, device 1 is comprised of a drug-
20 and permeation enhancer-containing reservoir ("drug reservoir") 2 which is
21 preferably in the form of a matrix containing the drug and the enhancer
22 dispersed therein. A backing layer 3 is provided adjacent one surface of drug
23 reservoir 2. Adhesive overlay 4 maintains the device 1 on the skin and may
24 be fabricated together with, or provided separately from, the remaining
25 elements of the device. With certain formulations, the adhesive overlay 4
26 may be preferable to an in-line contact adhesive, such as adhesive layer 28
27 as shown in FIG. 3. Backing layer 3 is preferably slightly larger than drug
28 reservoir 2, and in this manner prevents the materials in drug reservoir 2 from
29 adversely interacting with the adhesive in overlay 4. Reservoir 2 may be
30 either saturated, unsaturated, or contain an amount of drug in excess of

1 saturation. A strippable or removable liner 5 is also provided with device 1
2 and is removed just prior to application of device 1 to the skin.

3 Figure 2 illustrates another embodiment of the invention, device 10,
4 shown in placement on the skin 17. In this embodiment, the transdermal
5 delivery device 10 comprises a multi-laminate drug formulation/enhancer
6 reservoir 11 having at least two zones 12 and 14. Zone 12 consists of a drug
7 reservoir substantially as described with respect to FIG. 1. Zone 14
8 comprises a permeation enhancer reservoir which is preferably made from
9 substantially the same matrix as is used to form zone 12. Zone 14 comprises
10 the permeation enhancer dispersed throughout, preferably in excess of
11 saturation. A rate-controlling membrane 13 for controlling the release rate of
12 the permeation enhancer from zone 14 to zone 12 is placed between the two
13 zones. A rate-controlling membrane (not shown) for controlling the release
14 rate of the enhancer and/or drug from zone 12 to the skin may also optionally
15 be utilized and would be present between the skin 17 and zone 12.

16 The rate-controlling membrane may be fabricated from permeable,
17 semipermeable or microporous materials which are known in the art to control
18 the rate of agents into and out of delivery devices and having a permeability
19 to the permeation enhancer lower than that of zone 12. Suitable materials
20 include, but are not limited to, polyethylene, polyvinyl acetate and ethylene
21 vinyl acetate copolymers.

22 An advantage of the device described in FIG. 2 is that if zone 12
23 contains an excess of drug above saturation, the drug-loaded zone 12 is
24 concentrated at the skin surface rather than throughout the entire mass of the
25 reservoir 11. This functions to reduce the amount of drug in the device while
26 maintaining an adequate supply of the permeation enhancer or mixture.

27 Superimposed over the drug formulation/enhancer -reservoir 11 of
28 device 10 is a backing 15 and an adhesive overlay 16 as described above
29 with respect to FIG. 1. In addition, a strippable liner (not shown) would
30 preferably be provided on the device prior to use as described with respect to
31 FIG. 1 and removed prior to application of the device 10 to the skin 17.

1 In the embodiments of FIGS. 1 and 2, the carrier or matrix material
2 has sufficient viscosity to maintain its shape without oozing or flowing.
3 If, however, the matrix or carrier is a low viscosity flowable material,
4 the composition can be fully enclosed in a dense non-porous or microporous
5 skin-contacting membrane, as known to the art from U.S. Pat. No. 4,379,454
6 (not ed above), for example.

7 An example of a presently preferred transdermal delivery device is
8 illustrated in FIG. 3. In FIG. 3, transdermal delivery device 20 comprises a
9 drug reservoir 22 containing together the drug and the permeation enhancer.
10 Reservoir 22 is preferably in the form of a matrix containing the drug and the
11 enhancer dispersed therein. Reservoir 22 is sandwiched between a backing
12 layer 24, which is impermeable to both the drug and the enhancer, and an
13 in-line contact adhesive layer 28. In FIG. 3, the drug reservoir 22 is formed of
14 a material, such as a rubbery polymer, that is sufficiently viscous to maintain
15 its shape. The device 20 adheres to the surface of the skin 17 by means of
16 the contact adhesive layer 28. The adhesive for layer 28 should be chosen
17 so that it is compatible and does not interact with any of the drug or, in
18 particular, the permeation enhancer. The adhesive layer 28 may optionally
19 contain the permeation enhancer and/or drug. A strippable liner (not shown)
20 is normally provided along the exposed surface of adhesive layer 28 and is
21 removed prior to application of device 20 to the skin 17. In an alternative
22 embodiment, a rate-controlling membrane (not shown) is present and the
23 drug reservoir 22 is sandwiched between backing layer 24 and the rate-
24 controlling membrane, with adhesive layer 28 present on the skin - facing
25 side of the rate-controlling membrane.

26 Figure 4 depicts another preferred embodiment of the present
27 invention. Device 30 includes a matrix 31 comprising a pressure sensitive
28 adhesive, preferably a hydrophobic pressure sensitive adhesive, having drug
29 and the permeation enhancer dispersed therein and additionally includes a
30 backing layer 32 to contain the agent and prevent its loss. Matrix 31 also

1 preferably, but not necessarily, contains a water absorbing polymer to
2 improve the long term wearability of the matrix system. A release liner
3 (not shown in Figure 4) may also be included and is removed prior to
4 placing the device onto the skin 17.

5 Various materials suited for the fabrication of the various layers of the
6 transdermal devices of FIGS. 1-4 are known in the art or are disclosed in the
7 aforementioned transdermal device patents.

8 The matrix making up the drug / permeation enhancer reservoir can be
9 a gel or a polymer. Suitable materials should be compatible with the drug and
10 enhancer and any other components in the system. The matrix may be
11 aqueous or non-aqueous based. Aqueous formulations typically comprise
12 water or water/ethanol and about 1-5 wt% of a gelling agent, an example
13 being a hydrophilic polymer such as hydroxyethylcellulose or
14 hydroxypropylcellulose. Typical non-aqueous gels are comprised of silicone
15 fluid or mineral oil. Mineral oil based gels also typically contain 1-2 wt% of a
16 gelling agent such as colloidal silicon dioxide. The suitability of a particular
17 gel depends upon the compatibility of its constituents with the drug and the
18 permeation-enhancing mixture in addition to any other components in the
19 formulation. Suitable matrix materials include, without limitation, natural and
20 synthetic rubbers or other polymeric material, thickened mineral oil, or
21 petroleum jelly, for example.

22 Suitable non-aqueous based formulations for the reservoir matrix are
23 well known in the transdermal drug delivery art, and examples are listed in the
24 above named patents. A typical laminated system would consist essentially
25 of a polymeric membrane and/or matrix such as ethylene vinyl acetate (EVA)
26 copolymers, such as those described in US Patent No. 4,144,317, preferably
27 having a vinyl acetate content in the range of from about 9% to about 60%
28 and more preferably about 9% to 40% vinyl acetate. Polyisobutylene/oil
29 polymers containing from 4-25% high molecular weight polyisobutylene and

1 20-81% low molecular weight polyisobutylene with the balance being an oil
2 such as mineral oil or polyisobutylenes may also be used as the matrix
3 material.

4 In addition to a drug and permeation enhancer, which are essential to
5 the invention, the matrix may also contain water absorbing polymers such as
6 polyvinyl pyrrolidone, cross-linked polyvinyl pyrrolidone, polyaminoacrylates,
7 and polyvinyl alcohol, stabilizers, dyes, pigments, inert fillers, tackifiers,
8 excipients and other conventional components of transdermal delivery
9 devices as are known in the art.

10 The amounts of the drug that are present in the therapeutic device,
11 and that are required to achieve a therapeutic effect, depend on many
12 factors, such as the minimum necessary dosage of the particular drug; the
13 permeability of the matrix, of the adhesive layer and of the rate-controlling
14 membrane, if present; and the period of time for which the device will be fixed
15 to the skin. There is, in fact, no upper limit to the maximum amounts of drug
16 present in the device. The minimum amount of each drug is determined by
17 the requirement that sufficient quantities of drug must be present in the device
18 to maintain the desired rate of release over the given period of application.

19 The drug is generally dispersed through the matrix at a concentration
20 in excess of saturation in order to maintain unit activity throughout the
21 administration period. The amount of excess is determined by the intended
22 useful life of the system. However, the drug may be present at initial levels
23 below saturation without departing from this invention. Generally, the drug
24 may be present at initially subsaturated levels when: 1) the skin flux of the
25 drug is sufficiently low such that the reservoir drug depletion is slow and
26 small; 2) non-constant delivery of the drug is desired or acceptable; and/or
27 3) saturation or supersaturation of the reservoir is achieved in use by
28 cosolvent effects which change the solubility of the drug in use such as by
29 loss of a cosolvent or by migration of water into the reservoir.

1 The permeation enhancer is dispersed throughout the matrix,
2 preferably at a concentration sufficient to provide permeation-enhancing
3 concentrations of enhancer in the reservoir throughout the anticipated
4 administration period.

5 In the present invention, the drug is delivered through the skin or other
6 body surface at a therapeutically effective rate (that is, a rate that provides
7 an effective therapeutic result) and the permeation enhancer is delivered
8 at a permeation-enhancing rate (that is, a rate that provides increased
9 permeability of the application site to the drug) for a predetermined time
10 period.

11 A preferred embodiment of the present invention is a multilaminate
12 such as that illustrated in FIG. 3 (either with or without a rate-controlling
13 membrane) wherein reservoir 22 comprises, by weight, 30- 90% polymer
14 (preferably EVA with a vinyl acetate content of 40%), 0.01-40% drug, and
15 1-70% of a permeation enhancer according to Formula I. The in-line
16 adhesive layer 28 contains an adhesive which is compatible with the
17 permeation enhancer. In another preferred embodiment of the invention,
18 a multilaminate such as that in FIG. 3 includes reservoir 22 comprising,
19 by weight, 30-90% polymer (preferably EVA with a vinyl acetate content
20 of 40%), 0.01-40% drug, 1-70% of a permeation enhancer according to
21 Formula I, and 1-60% of a second permeation enhancer, preferably GML
22 or ethanol.

23 The devices of this invention can be designed to effectively deliver a
24 drug for an extended time period of up to 7 days or longer. Seven days is
25 generally the maximum time limit for application of a single device because
26 the skin site may be affected by a period of occlusion greater than 7 days,
27 or other problems such as the system or edges of the system lifting off of the
28 skin may be encountered over such long periods of application. Where it is
29 desired to have drug delivery for greater than 7 days (such as, for example,
30 when a hormone is being applied for a contraceptive effect), when one device

1 has been in place on the skin for its effective time period, it is replaced with a
2 fresh device, preferably on a different skin site.

3 The transdermal therapeutic devices of the present invention are
4 prepared in a manner known in the art, such as by those procedures, for
5 example, described in the transdermal device patents listed previously herein.

6 The following examples are offered to illustrate the practice of the
7 present invention and are not intended to limit the invention in any manner.

8 EXAMPLE 1

9 Various ethanol / tetraethylene glycol monododecyl ether (laureth-4)
10 (Heterene Chemical Co., Patterson, N.J.) mixture donor compositions having
11 different amounts of ethanol and laureth-4 were tested with testosterone
12 to measure their effect upon drug flux across human cadaver epidermis at
13 35° C. All donor compositions were saturated with the drug. Test data were
14 obtained using a 1.13 cm² wet-wet horizontal flux cell with 0.2 ml donor
15 solution and 20 ml receptor solution (pH 7.4 phosphate buffer, 0.05 M).
16 Total drug permeated was measured and the results are presented in Fig. 5.
17 As seen in Fig. 5, 30 wt% laureth-4 alone exhibited about a four fold increase
18 in testosterone permeation compared to the sample without any permeation
19 enhancer.

TABLE 1

Measured and predicted cumulative release ($\mu\text{g}/\text{cm}^2 \cdot 24 \text{ hr}$)
from donor solutions of various ethanol and laureth-4 content

laureth-4 wt%	ethanol wt%	measured release	predicted release
0	0	5	-
20	0	15	-
30	0	20	-
40	0	16	-
0	20	15	-
0	40	18	-
0	50	21	-
20	20	20	30
20	40	32	33
20	50	50	36
30	20	25	35
30	40	40	38
30	50	60	41
40	20	26	31
40	40	39	34
40	50	52	37

Table 1 lists the formulations including the amounts of ethanol and laureth-4 and the observed cumulative release of testosterone over a 24 hour period. Table 1 also provides a predicted cumulative release of testosterone which is the sum of that observed from the formulations including the corresponding amounts of laureth-4 or ethanol alone. As seen from Table 1, the enhancement of testosterone permeation in the presence of both ethanol and laureth-4 showed a more than additive effect of the results obtained from the sum of the cumulative amount permeated from each of these enhancers individually when the ethanol was present at about 40 wt% or greater.

EXAMPLE 2

Transdermal systems were prepared to measure the flux of oxybutynin through human epidermis. The oxybutynin/permeation enhancer reservoir was prepared by mixing ethylene vinyl acetate copolymer having a vinyl acetate content of 40 percent ("EVA 40", U.S.I. Chemicals, Illinois) in an

1 internal mixer (Brabender type mixer) until the EVA 40 pellets fused.
2 Oxybutynin, glycerol monolaurate (Danisco Ingredients USA, Inc., New
3 Century, Kansas) and either diethylene glycol monododecyl ether (laureth-2)
4 (Heterene Chemical Co., Patterson, N.J.) or lauryl lactate (ISP Van Dyk,
5 Bellevue, NJ) were then added. The oxybutynin/enhancer reservoir
6 formulation is shown in Table 2.

7 The mixture was blended, cooled, and calendered to a 5 mil thick film.
8 The drug reservoir film was then laminated to a Sontara® (DuPont,
9 Wilmington, DE) backing on its skin distal surface and a Celgard® (Hoescht
10 Celanese, Charlotte, NC) microporous polypropylene membrane on its skin
11 facing surface. An acrylic contact adhesive (MSP041991P, 3M) was then
12 laminated to the microporous polypropylene membrane. The laminate was
13 then cut into 1.98 cm² circles using a stainless steel punch and placed in a
14 35 °C oven to equilibrate. Systems were then masked to prevent any part of
15 the system other than the skin contacting surface to be exposed to the
16 receptor solution when performing the skin flux experiments.

17 **TABLE 2**
18 **Drug Reservoir Formulation (wt%)**

Oxybutynin	GML	lauryl lactate	laureth-2	EVA 40
20	25	12	-	43
20	25	-	12	43

19 The in vitro transdermal oxybutynin permeation rates through the
20 epidermis of two human skin donors from the systems described above were
21 determined. For each system tested, the release liner was removed and the
22 oxybutynin-releasing surface was centered and placed against the stratum
23 corneum side of a disc of human epidermis which had been blotted dry just
24 prior to use. The excess epidermis was wrapped around the device so that
25 none of the device edge was exposed to the receptor solution.

26 The assembly was then attached to the flat side of a Teflon® holder
27 of a release rate rod using wire and nylon mesh. The rod with the system
28 attached was placed into a 50 cc test tube filled with a known volume of

1 receptor solution (0.05M phosphate solution, pH 6.0). Constant vertical
2 stirring was accomplished by attaching the rod to a crossrod connected to
3 an agitator that reciprocates the rod and system vertically in the test tube.
4 The receptor solution was maintained at 35 °C.

5 At given time intervals, the entire receptor solution was removed from
6 the test tube and replaced with an equal volume of fresh receptor solution
7 previously equilibrated at 35 °C. The receptor solutions were stored in
8 capped vials at 4 °C until assayed for oxybutynin content by HPLC. From the
9 drug concentration and the volume of receptor solution, the area of
10 permeation and the time interval, the flux of the drug through the epidermis
11 was calculated as follows: (drug concentration x volume of receptor solution) /
12 (area x time) = flux ($\mu\text{g}/\text{cm}^2 \cdot \text{hr}$). The results are depicted in Figure 6, which
13 shows that the system comprising the GML/laureth-2 mixture resulted in the
14 longer maintenance of a higher flux than the GML/lauryl lactate system.

15

16

EXAMPLE 3

17

18 Control formulations containing drug in a matrix of EVA 40 were
19 prepared by dissolving the drug and EVA 40 in tetrahydrofuran (THF). The
20 solution was poured onto an FCD / polyester release liner to evaporate. The
21 dried material was then pressed to 4-5 mils thickness between two sheets of
22 FCD / polyester release liner at 75° C. The resulting film was heat-laminated
23 to an impermeable backing (Medpar or Scotchpak, for example), and 1.6 cm²
discs were punched out or die-cut from the laminate.

24

25 Test formulations containing laureth-2 benzoate (Bernel Chemical Co.,
26 Englewood, N.J.) or laureth-2 acetate (Phoenix Chemical Co., Inc.,
27 Somerville, N.J.) in addition to the drug and EVA 40 were prepared by
28 dissolving the necessary components in THF and following the same
29 procedures as for the control formulations. The compositions of the test
formulations and controls are shown in Table 3.

TABLE 3
Laureth-2 acetate and Laureth-2 benzoate
Test and Control Formulations

Formulation	Drug	wt%	Permeation Enhancer	wt%	EVA 40 wt%
a	oxybutynin	25	laureth-2 benzoate	25	50
b	oxybutynin	25	-	-	75
c	melatonin	10	laureth-2 acetate	25	65
d	melatonin	10	-	-	90
e	ketorolac	7	laureth-2 benzoate	25	68
f	ketorolac	10	-	-	90
g	ketorolac	7	laureth-2 acetate	25	68
h	ketorolac	10	-	-	90
i	testosterone	10	laureth-2 benzoate	25	65
j	testosterone	2	-	-	98
k	testosterone	10	laureth-2 acetate	25	65
l	testosterone	2	-	-	98

The in vitro transdermal flux of oxybutynin, melatonin, ketorolac, and testosterone with either laureth-2 acetate or laureth-2 benzoate was compared to the no-enhancer control using the in vitro skin flux experiment described in Example 2 above. The results are depicted in Figures 7-12, which show that both laureth-2 acetate and laureth-2 benzoate increased significantly the skin permeability to these drugs.

EXAMPLE 4

Control formulations containing drug in a matrix of EVA 40 were prepared as described in Example 3. Test formulations containing laureth-3 carboxylic acid (L-3 carboxylic acid) (Huls America Inc., Piscataway, N.J.) or laureth-5 carboxylic acid (L-5 carboxylic acid) (Huls America Inc., Piscataway, N.J.) in addition to the drug and EVA 40 were prepared by dissolving the necessary components in THF and following the same procedures as for the control formulations. The compositions of the test formulations and controls are shown in Table 4.

TABLE 4
Laureth-3 carboxylic acid and Laureth-5 carboxylic acid
Test and Control Formulations

Formulation	Drug	wt%	Permeation Enhancer	wt%	EVA 40 wt%
A	oxybutynin	25	L-3 carboxylic acid	25	50
B	oxybutynin	25	-	-	75
C	oxybutynin	10	L-5 carboxylic acid	25	65
D	oxybutynin	10	-	-	90
E	ketorolac	7	L-3 carboxylic acid	25	68
F	ketorolac	10	-	-	90
G	ketorolac	7	L-5 carboxylic acid	25	68
H	ketorolac	10	-	-	90
I	alprazolam	15	L-3 carboxylic acid	25	60
J	alprazolam	15	-	-	85
K	alprazolam	15	L-5 carboxylic acid	25	60
L	alprazolam	15	-	-	85

The in vitro transdermal flux of oxybutynin, alprazolam, and ketorolac, with either L-5 carboxylic acid or L-3 carboxylic acid was compared to the no-enhancer control using the in vitro skin flux experiment described in Example 2 above. The results are depicted in Figures 13-18, which show that both L-5 carboxylic acid and L-3 carboxylic acid increased significantly the skin permeability to these drugs.

This invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

1 What is claimed is:

2

3 1. A composition of matter for increasing the permeability of a body
4 surface or membrane to at least one drug comprising said drug in
5 combination with a permeation enhancer of the formula:



7 wherein $n = 3-19$; $m = 1-20$; and $R = \text{i)H}$; ii) CH_2COOH ; or iii) OC-R'

8 where R' is an alkyl or aryl group comprising 1-16 carbons, said permeation
9 enhancer present in a permeation-enhancing amount sufficient to
10 substantially increase the permeability of the body surface or membrane to at
11 least one drug in order to deliver said drug to an individual at a therapeutically
12 effective rate.

13 2. A composition according to claim 1 wherein the permeation
14 enhancer and at least one drug are dispersed within a pharmaceutically
15 acceptable carrier.

16 3. A composition according to claim 1 wherein the permeation
17 enhancer is an alkoxyated alcohol comprising a medium chain fatty acid and
18 an oligomer of polyethylene oxide wherein $n=3-15$ and $m=1-8$.

19 4. A composition according to claim 3 wherein the permeation
20 enhancer is a polyethyleneglycol monolauryl ether.

21 5. A composition according to claim 4 wherein the permeation
22 enhancer is selected from diethylene glycol monododecyl ether and
23 tetraethylene glycol monododecyl ether.

24 6. A composition according to claim 1 wherein the permeation
25 enhancer is a an alkyl or aryl carboxylic acid ester of polyethyleneglycol
26 monoalkyl ether.

27 7. A composition according to claim 6 wherein the permeation
28 enhancer is a carboxylic acid ester of polyethyleneglycol monolauryl ether.

29 8. A composition according to claim 7 wherein the permeation
30 enhancer is selected from diethylene glycol monododecyl ether-acetate and
31 diethylene glycol monododecyl ether-benzoate.

1 9. A composition according to claim 1 wherein the permeation
2 enhancer is a polyethyleneglycol alkyl carboxymethyl ether.

10. A composition according to claim 9 wherein the permeation enhancer is a polyethyleneglycol lauryl carboxymethyl ether.

11. A composition according to claim 10 wherein the permeation enhancer is selected from triethylene glycol monododecyl ether-carboxylic acid and polyethylene glycol monododecyl ether-carboxylic acid.

12. A composition according to claim 1 wherein the permeation enhancer is combined with a permeation-enhancing amount of one or more permeation enhancers selected from monoglycerides or mixtures of monoglycerides of fatty acids, lauramide diethanolamine, lower C₁₋₄ alcohols, alkyl laurates, acyl lactylates, dodecyl acetate, and C₁₀ - C₂₀ fatty acid esters.

13 13. A composition according to claim 12 wherein the permeation
14 enhancer is combined with a permeation-enhancing amount of one or more
15 permeation enhancers selected from glycerol monolaurate, glycerol
16 monooleate, glycerol monolinoleate, lauramide diethanolamine, ethanol,
17 methyl laurate, caproyl lactic acid, lauroyl lactic acid, dodecyl acetate, and
18 lauryl lactate.

19 14. A composition according to claim 12 wherein the permeation
20 enhancer is combined with a permeation-enhancing amount of glycerol
21 monolaurate.

22 15. A device for the transdermal administration of at least one drug
23 to an individual at a therapeutically effective rate, by permeation through a
24 body surface or membrane, comprising:

(a) a reservoir comprising at least one drug and a permeation enhancing-amount of a permeation enhancer of the formula



wherein n = 3-19; m = 1-20; and R = i) OH; ii) OCH₂COOH; or iii) OOC-
R' where R' is an alkyl or aryl group comprising 1-16 carbons, said
permeation enhancer present in a permeation-enhancing amount

1 sufficient to substantially increase the permeability of the body surface or
2 membrane to at least one drug in order to deliver said drug to an individual at
3 a therapeutically effective rate; and

4 (b) means for maintaining said reservoir in drug- and permeation
5 enhancer- transmitting relation with the body surface or membrane, wherein
6 said drug is delivered to a patient at a therapeutically effective rate.

7 16. A device according to claim 15 wherein the permeation
8 enhancer is an alkoxylated alcohol comprising a medium chain fatty acid and
9 an oligomer of polyethylene oxide wherein $n=3-15$ and $m=1-8$.

10 17. A device according to claim 16 wherein the permeation
11 enhancer is a polyethyleneglycol monolauryl ether.

12 18. A device according to claim 17 wherein the permeation
13 enhancer is selected from diethylene glycol monododecyl ether and
14 tetraethylene glycol monododecyl ether.

15 19. A device according to claim 15 wherein the permeation
16 enhancer is a an alkyl or aryl carboxylic acid ester of polyethyleneglycol
17 monoalkyl ether.

18 20. A device according to claim 19 wherein the permeation
19 enhancer is a carboxylic acid ester of polyethyleneglycol monolauryl ether.

20 21. A device according to claim 20 wherein the permeation
21 enhancer is selected from diethylene glycol monododecyl ether-acetate and
22 diethylene glycol monododecyl ether-benzoate.

23 22. A device according to claim 15 wherein the permeation
24 enhancer is a polyethyleneglycol alkyl carboxymethyl ether.

25 23. A device according to claim 22 wherein the permeation
26 enhancer is a polyethyleneglycol lauryl carboxymethyl ether.

27 24. A device according to claim 23 wherein the permeation
28 enhancer is selected from triethylene glycol monododecyl ether-carboxylic
29 acid and polyethylene glycol monododecyl ether-carboxylic acid.

25. A device according to claim 15 wherein the permeation enhancer is combined with a permeation-enhancing amount of one or more of the permeation enhancers selected from monoglycerides or mixtures of monoglycerides of fatty acids, lauramide diethanolamine, lower C₁₋₄ alcohols, alkyl laurates, acyl lactylates, dodecyl acetate, and C₁₀ - C₂₀ fatty acid esters.

26. A device according to claim 25 wherein the permeation enhancer is combined with a permeation-enhancing amount of one or more permeation enhancers selected from glycerol monolaurate, glycerol monooleate, glycerol monolinoleate, lauramide diethanolamine, ethanol, methyl laurate, caproyl lactic acid, lauroyl lactic acid, dodecyl acetate, and lauryl lactate.

12 27. A device according to claim 25 wherein the permeation
13 enhancer is combined with a permeation-enhancing amount of glycerol
14 monolaurate.

15 28. A device according to claim 15 wherein the drug is selected
16 from testosterone, nandrolone, alprazolam, oxybutynin, ketorolac, and
17 melatonin.

29. A device for the transdermal administration of at least one drug to an individual at a therapeutically effective rate, by permeation through a body surface or membrane, comprising:

(a) a first reservoir comprising at least one drug and a permeation-enhancing amount of a permeation enhancer of the formula



24 wherein n = 3-19; m = 1-20; and R = i) H; ii) CH₂COOH; or iii) OC-R'
25 where R' is an alkyl or aryl group comprising 1-16 carbons;

(b) a second reservoir adjacent the skin-distal surface of the first reservoir comprising an additional amount of said permeation enhancer and substantially free of said drug in excess of saturation;

1 (c) means for maintaining said first and second reservoirs in drug- and
2 permeation enhancer- transmitting relation with the body surface or
3 membrane, wherein the drug is delivered to a patient at a therapeutically
4 effective rate.

5 30. A device according to claim 29 further comprising a rate
6 controlling membrane positioned between the first and second reservoirs.

7 31. A device according to claim 29 wherein the permeation
8 enhancer is an alkoxyated alcohol comprising a medium chain fatty acid and
9 an oligomer of polyethylene oxide wherein $n=3-15$ and $m=1-8$.

10 32. A device according to claim 31 wherein the permeation
11 enhancer is a polyethyleneglycol monolauryl ether.

12 33. A device according to claim 32 wherein the permeation
13 enhancer is selected from diethylene glycol monododecyl ether and
14 tetraethylene glycol monododecyl ether.

15 34. A device according to claim 29 wherein the permeation
16 enhancer is a an alkyl or aryl carboxylic acid ester of polyethyleneglycol
17 monoalkyl ether.

18 35. A device according to claim 34 wherein the permeation
19 enhancer is a carboxylic acid ester of polyethyleneglycol monolauryl ether.

20 36. A device according to claim 35 wherein the permeation
21 enhancer is selected from diethylene glycol monododecyl ether-acetate and
22 diethylene glycol monododecyl ether-benzoate.

23 37. A device according to claim 29 wherein the permeation
24 enhancer is a polyethyleneglycol alkyl carboxymethyl ether.

25 38. A device according to claim 37 wherein the permeation
26 enhancer is a polyethyleneglycol lauryl carboxymethyl ether.

27 39. A device according to claim 38 wherein the permeation
28 enhancer is selected from triethylene glycol monododecyl ether-carboxylic
29 acid and polyethylene glycol monododecyl ether-carboxylic acid.

1 40. A device according to claim 29 wherein the permeation
2 enhancer is combined with a permeation-enhancing amount of one or more of
3 the permeation enhancers selected from monoglycerides or mixtures of
4 monoglycerides of fatty acids, lauramide diethanolamine, lower C₁₋₄ alcohols,
5 alkyl laurates, acyl lactylates, dodecyl acetate, and C₁₀ - C₂₀ fatty acid esters.

6 41. A device according to claim 40 wherein the permeation
7 enhancer is combined with a permeation-enhancing amount of one or more
8 permeation enhancers selected from glycerol monolaurate, glycerol
9 monooleate, glycerol monolinoleate, lauramide diethanolamine, ethanol,
10 methyl laurate, caproyl lactic acid, lauroyl lactic acid, dodecyl acetate, and
11 lauryl lactate.

12 42. A device according to claim 40 wherein the permeation
13 enhancer is combined with a permeation-enhancing amount of glycerol
14 monolaurate.

15 43. A device according to claim 29 wherein the drug is selected
16 from testosterone, nandrolone, alprazolam, oxybutynin, ketorolac, and
17 melatonin.

18 44. A method for the transdermal administration of at least one drug
19 to an individual, at a therapeutically effective rate, by permeation through a
20 body surface or membrane, comprising:

21 simultaneously administering, to the body surface or membrane :

22 (a) at least one drug; and

23 (b) a permeation enhancer of the formula



25 wherein n = 3-19; m = 1-20; and R = i) H; ii) CH₂COOH; or iii) OC-R'

26 where R' is an alkyl or aryl group comprising 1-16 carbons, at a permeation -
27 enhancing rate sufficient to substantially increase the permeability of the body
28 surface or membrane to the drug in order to deliver said drug to an individual
29 at a therapeutically effective rate.

1 45. A method according to claim 44 further comprising
2 simultaneously coadministering, at a permeation-enhancing rate, one or more
3 of the permeation enhancers selected from monoglycerides or mixtures of
4 monoglycerides of fatty acids, lauramide diethanolamine, lower C₁₋₄ alcohols,
5 alkyl laurates, acyl lactylates, dodecyl acetate, and C₁₀ - C₂₀ fatty acid esters.

6 46. A method according to claim 44 wherein the permeation
7 enhancer is selected from alkoxyated alcohols comprising a medium chain
8 fatty acid and an oligomer of polyethylene oxide wherein n=3-15 and m=1-8,
9 alkyl or aryl carboxylic acid esters of polyethyleneglycol monoalkyl ether, and
10 polyethyleneglycol alkyl carboxymethyl ethers.

11 47. A method according to claim 46 wherein the permeation
12 enhancer is selected from diethylene glycol monododecyl ether, tetraethylene
13 glycol monododecyl ether, diethylene glycol monododecyl ether acetate,
14 diethylene glycol monododecyl ether benzoate, triethylene glycol
15 monododecyl ether carboxylic acid, and polyethylene glycol monododecyl
16 ether carboxylic acid.

17 48. A method according to claim 45 wherein the permeation
18 enhancer is combined with a permeation-enhancing amount of one or more
19 permeation enhancers selected from glycerol monolaurate, glycerol
20 monooleate, glycerol monolinoleate, lauramide diethanolamine, ethanol,
21 methyl laurate, caproyl lactic acid, lauroyl lactic acid, dodecyl acetate, and
22 lauryl lactate.

23 49. A method according to claim 45 wherein the permeation
24 enhancer is combined with a permeation-enhancing amount of glycerol
25 monolaurate.

26 50. A method according to claim 44 wherein the drug is selected
27 from testosterone, alprazolam, oxybutynin, ketorolac, melatonin, and
28 nandrolone.

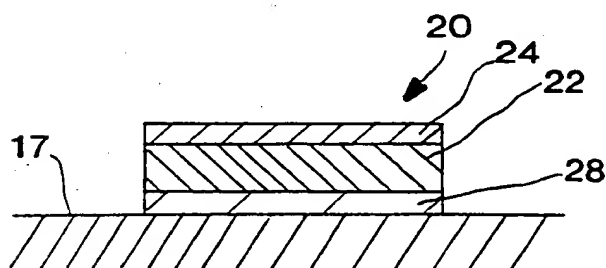
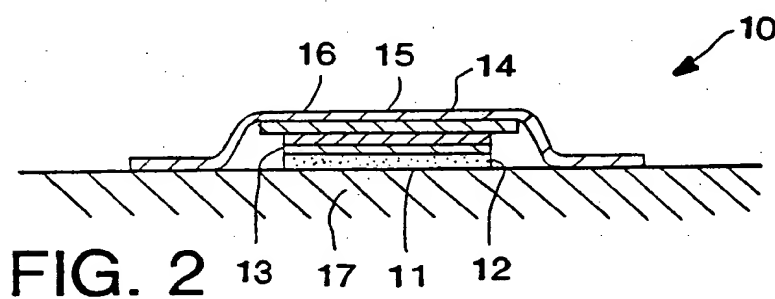
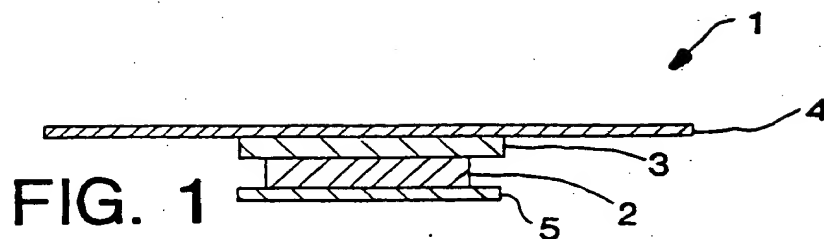


FIG. 3

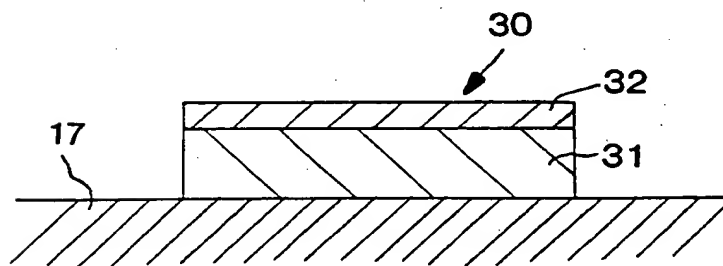


FIG. 4

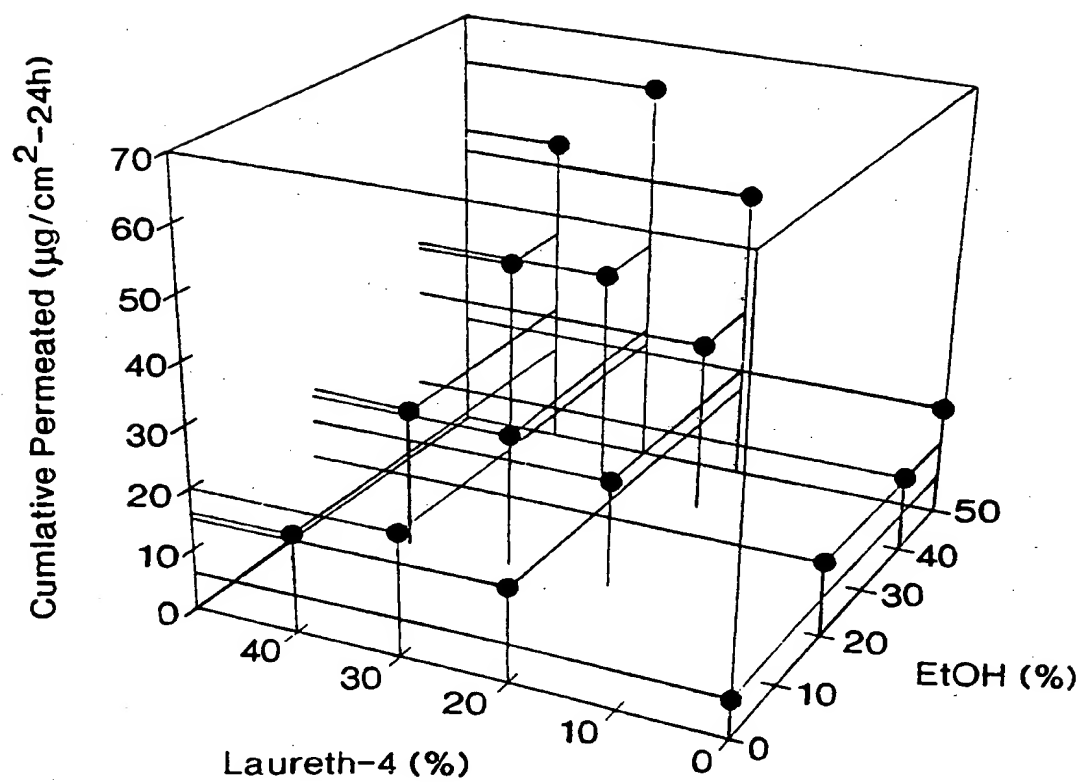


FIG. 5

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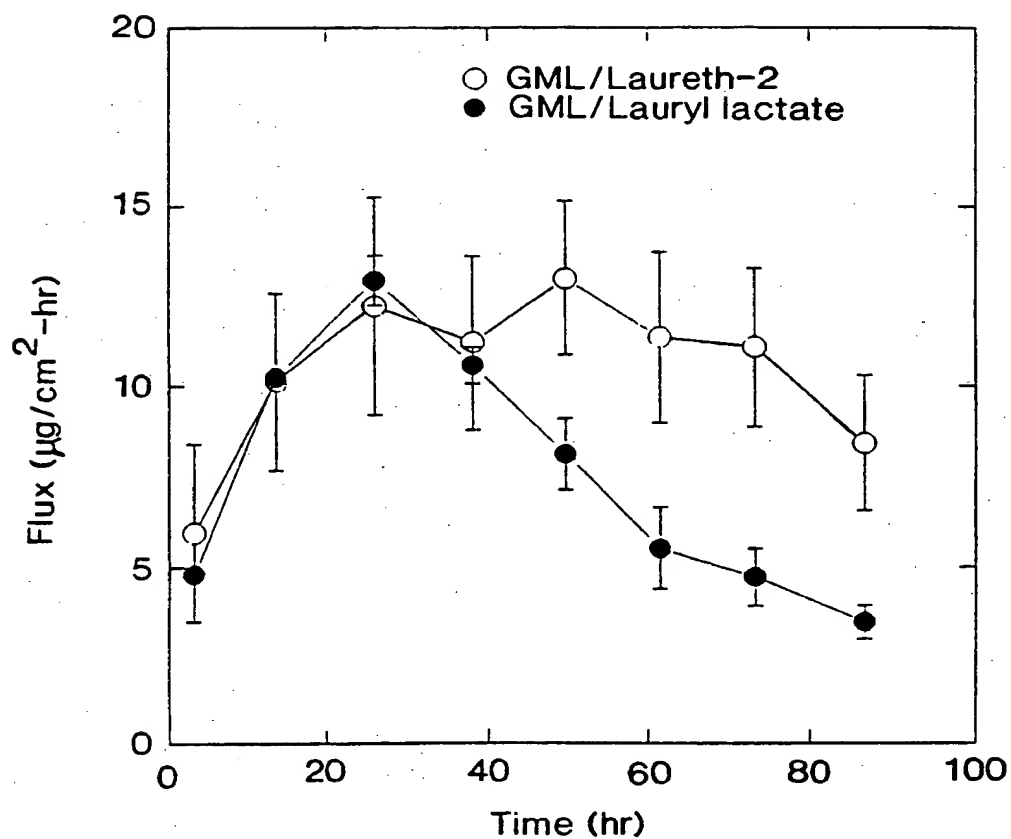


FIG. 6

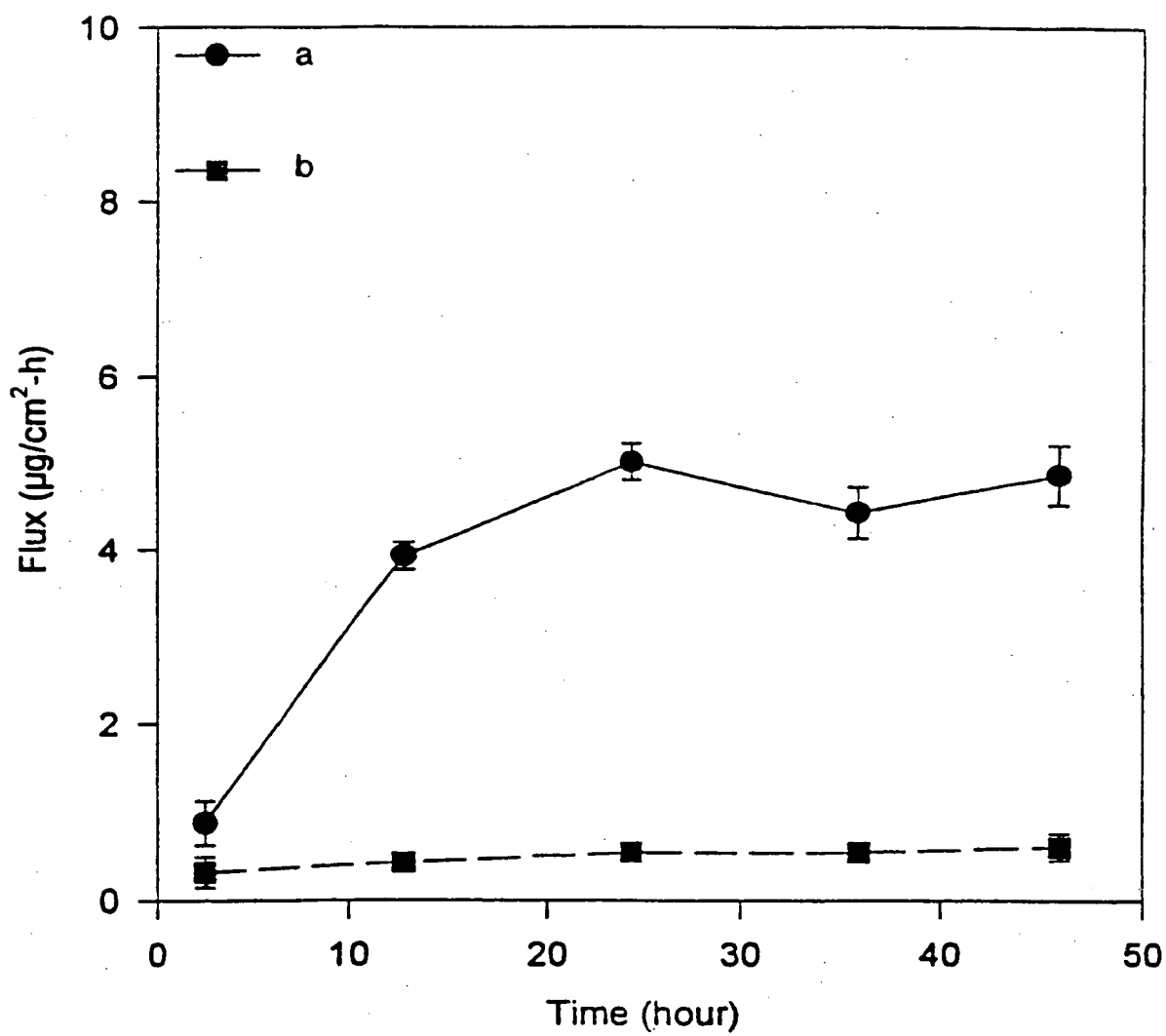


FIG. 7

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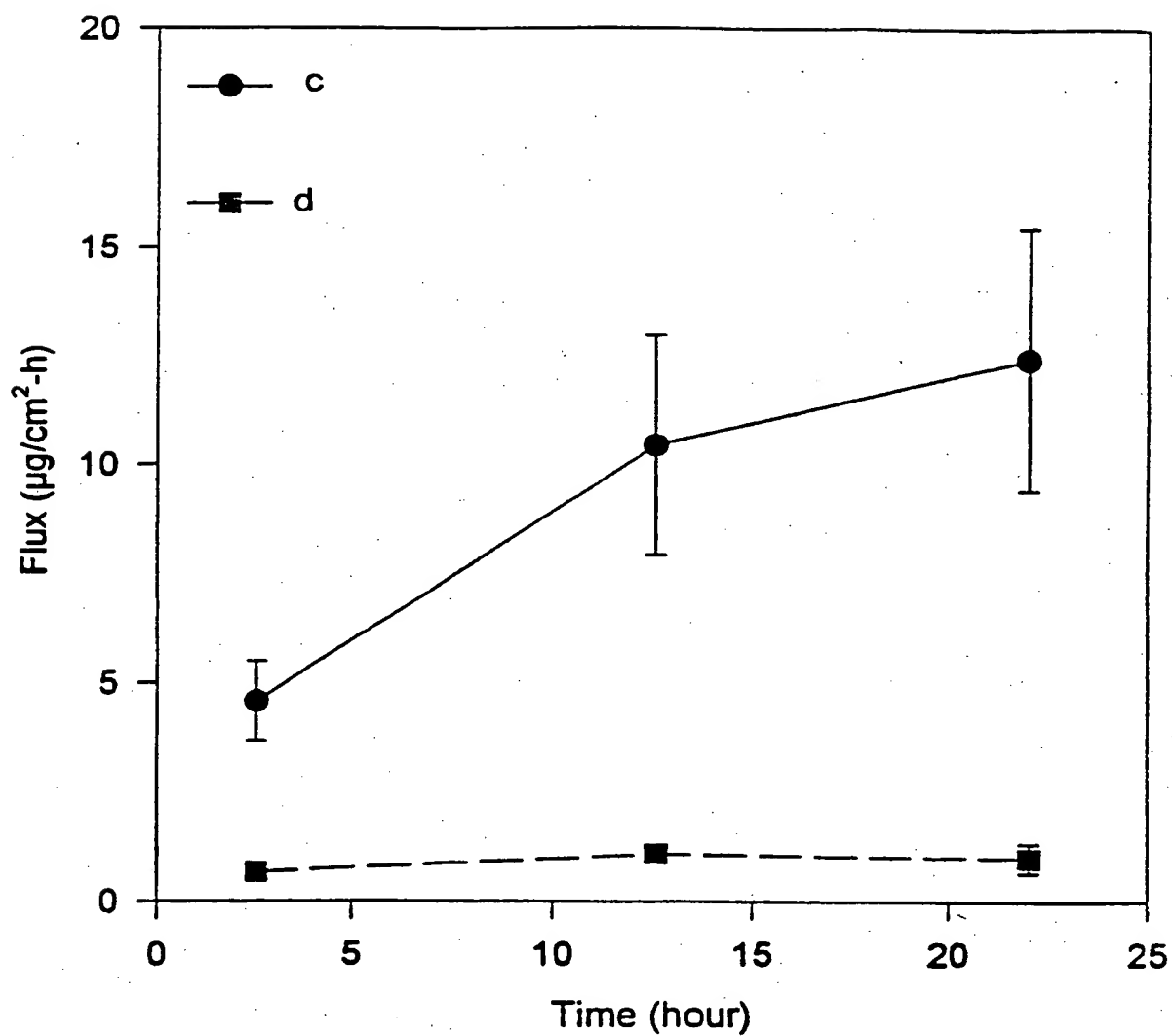


FIG. 8

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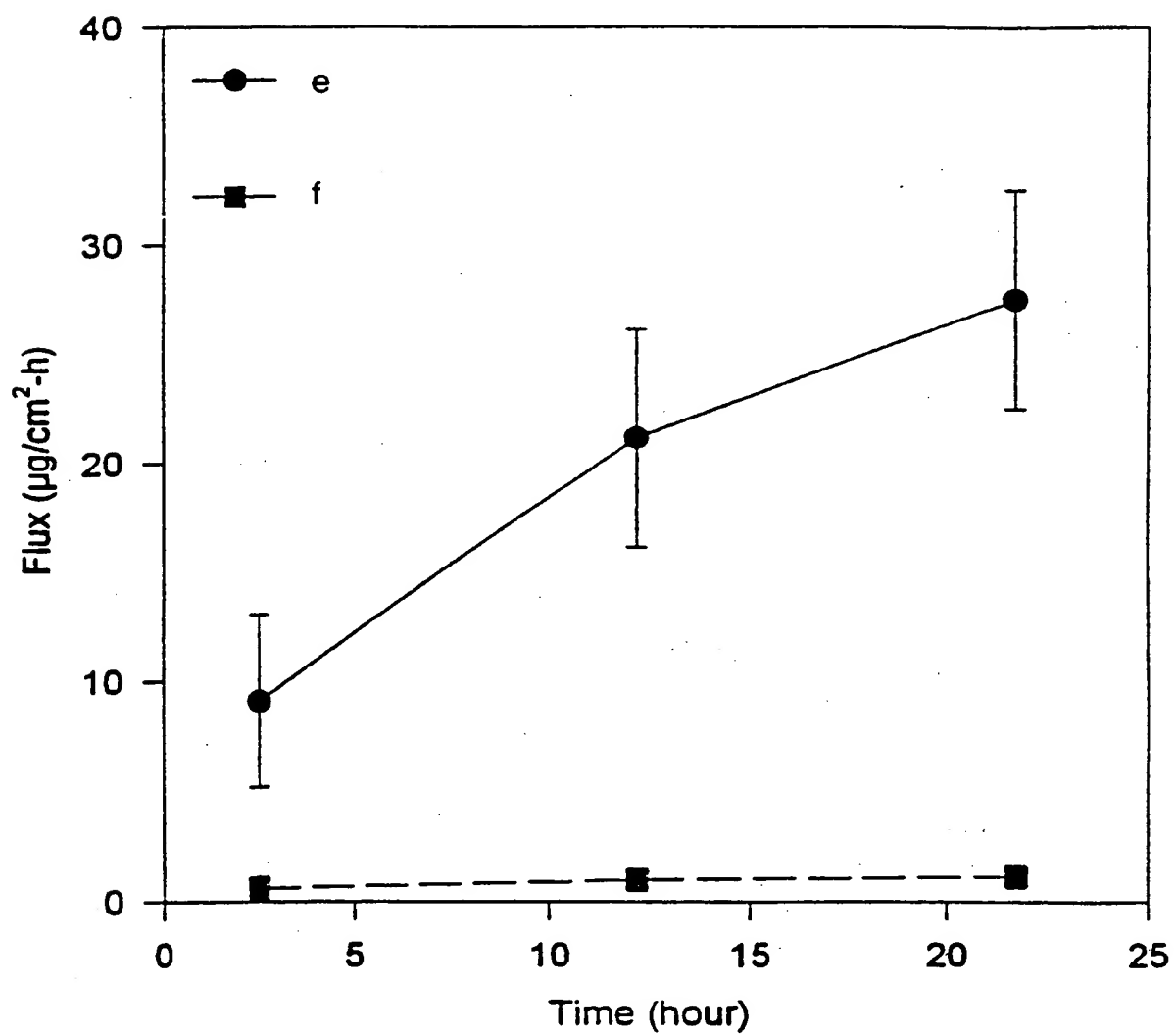


FIG. 9

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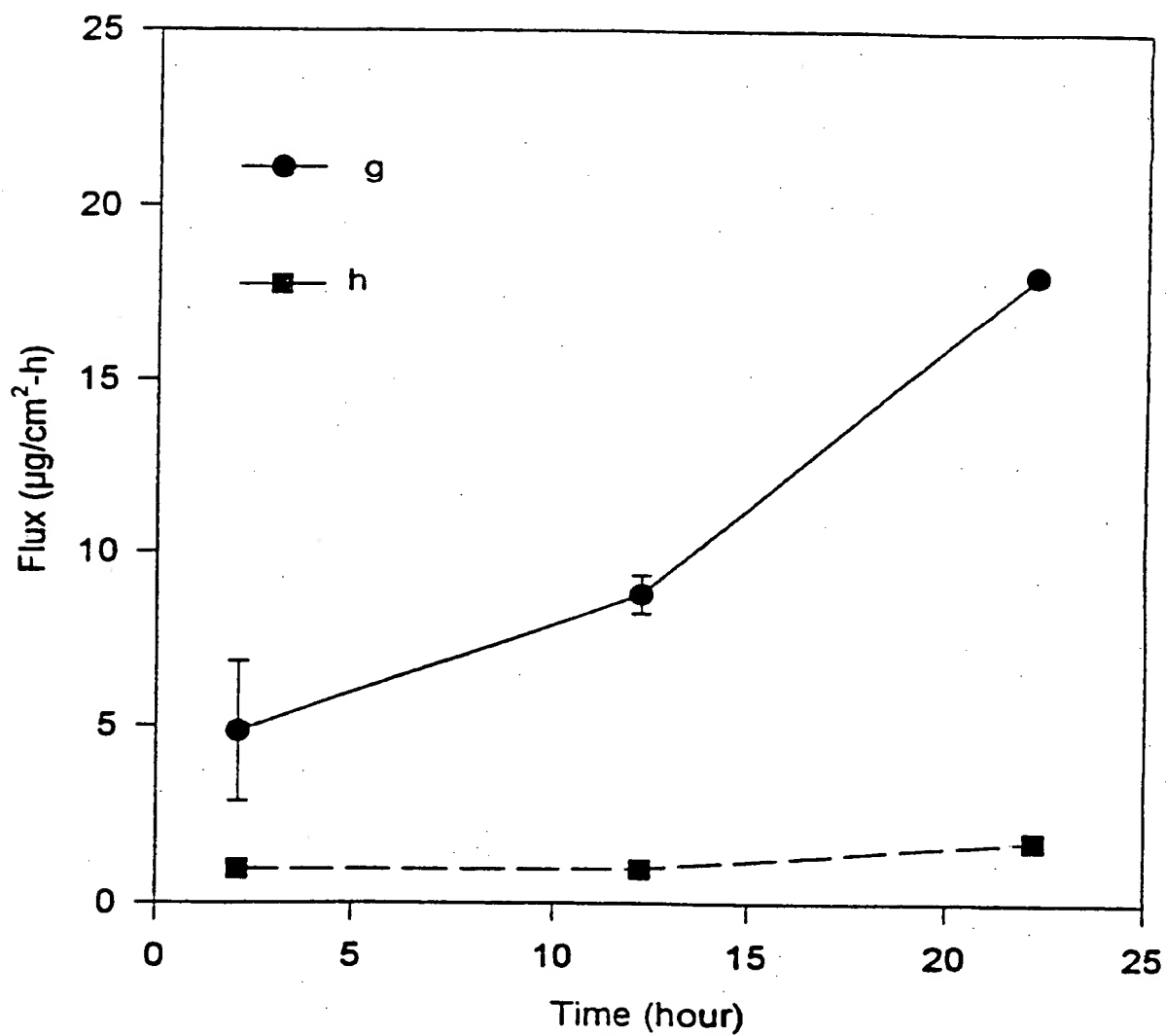


FIG. 10

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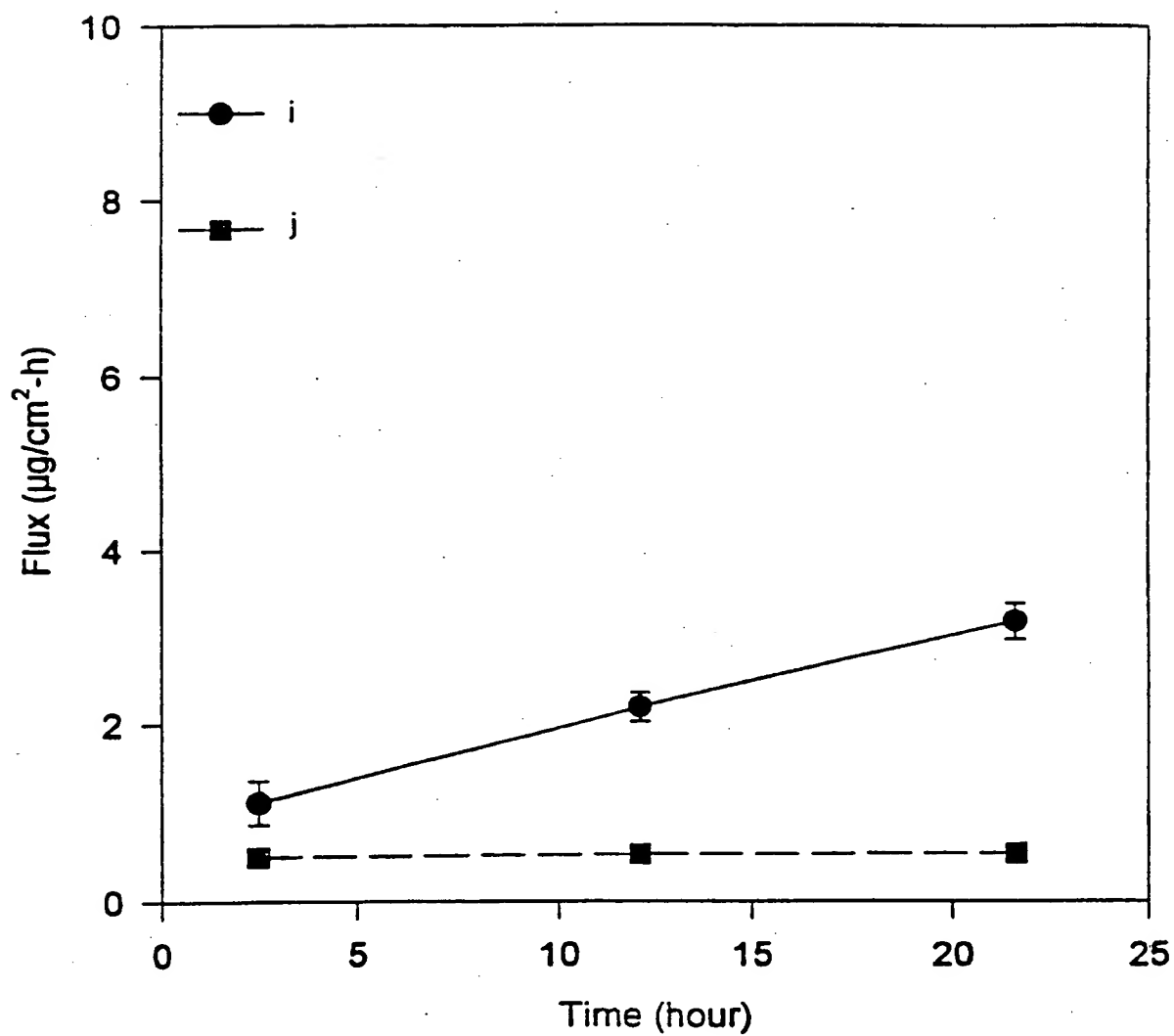


FIG. 11

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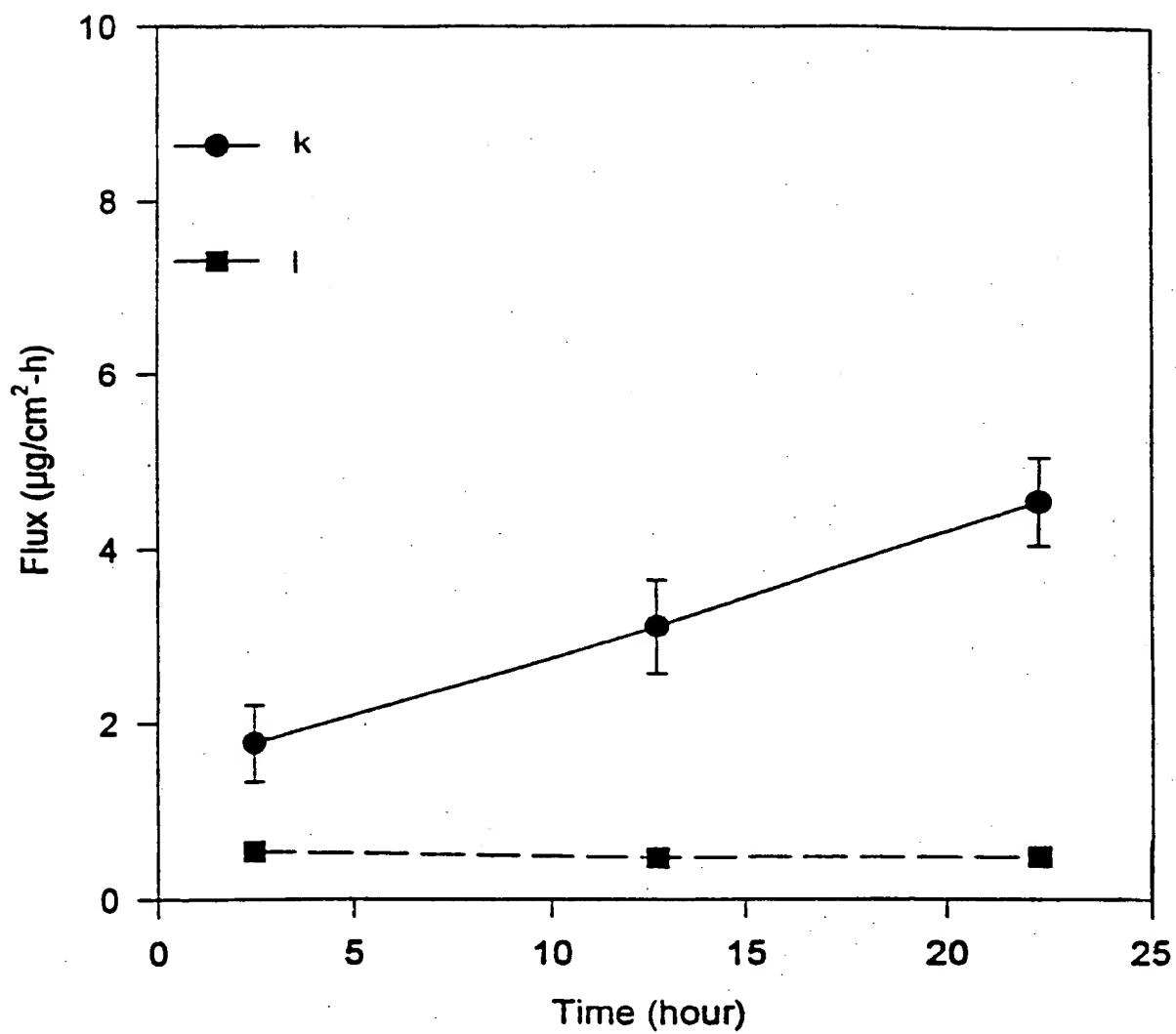


FIG. 12

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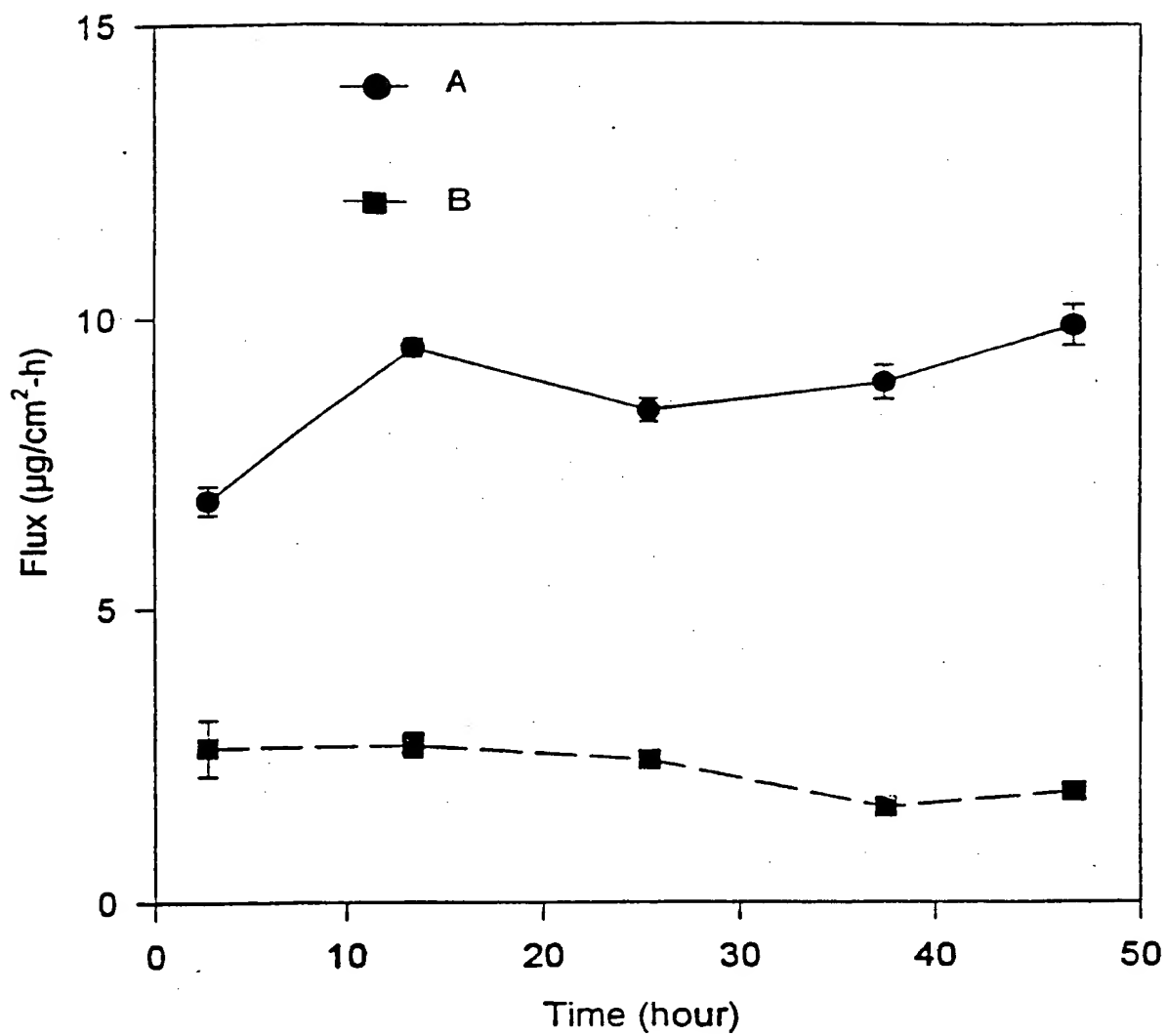


FIG. 13

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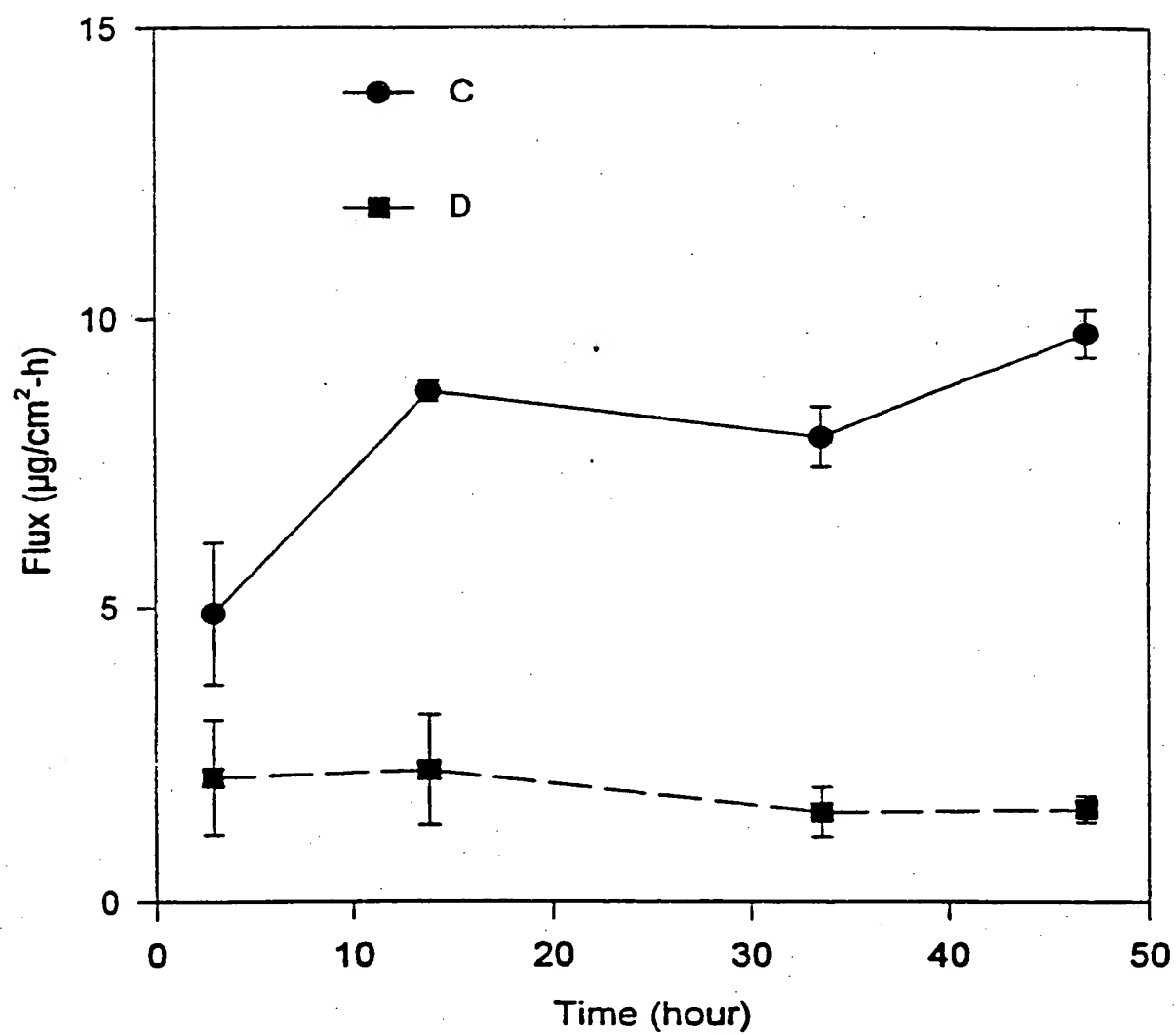


FIG. 14

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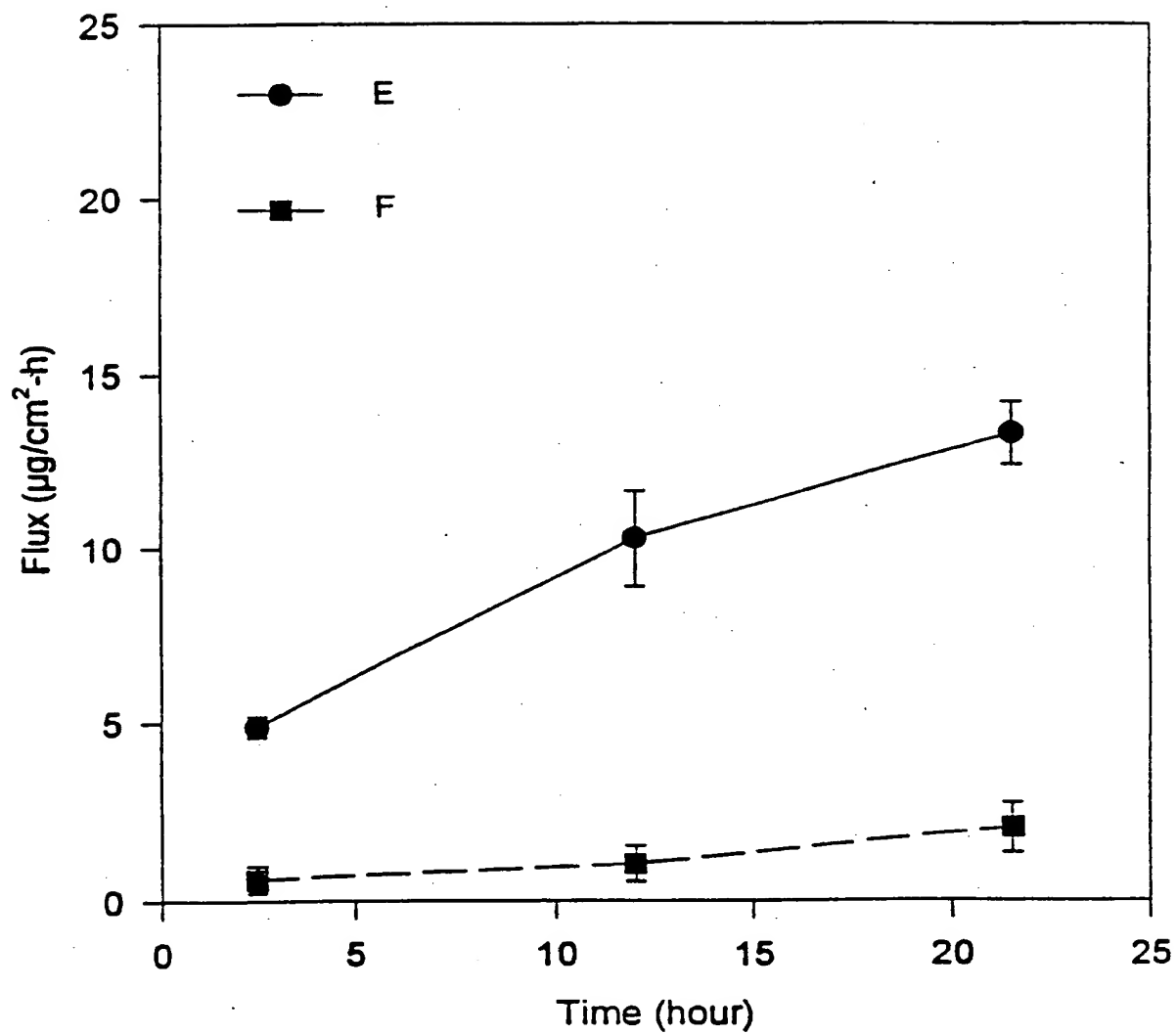


FIG. 15

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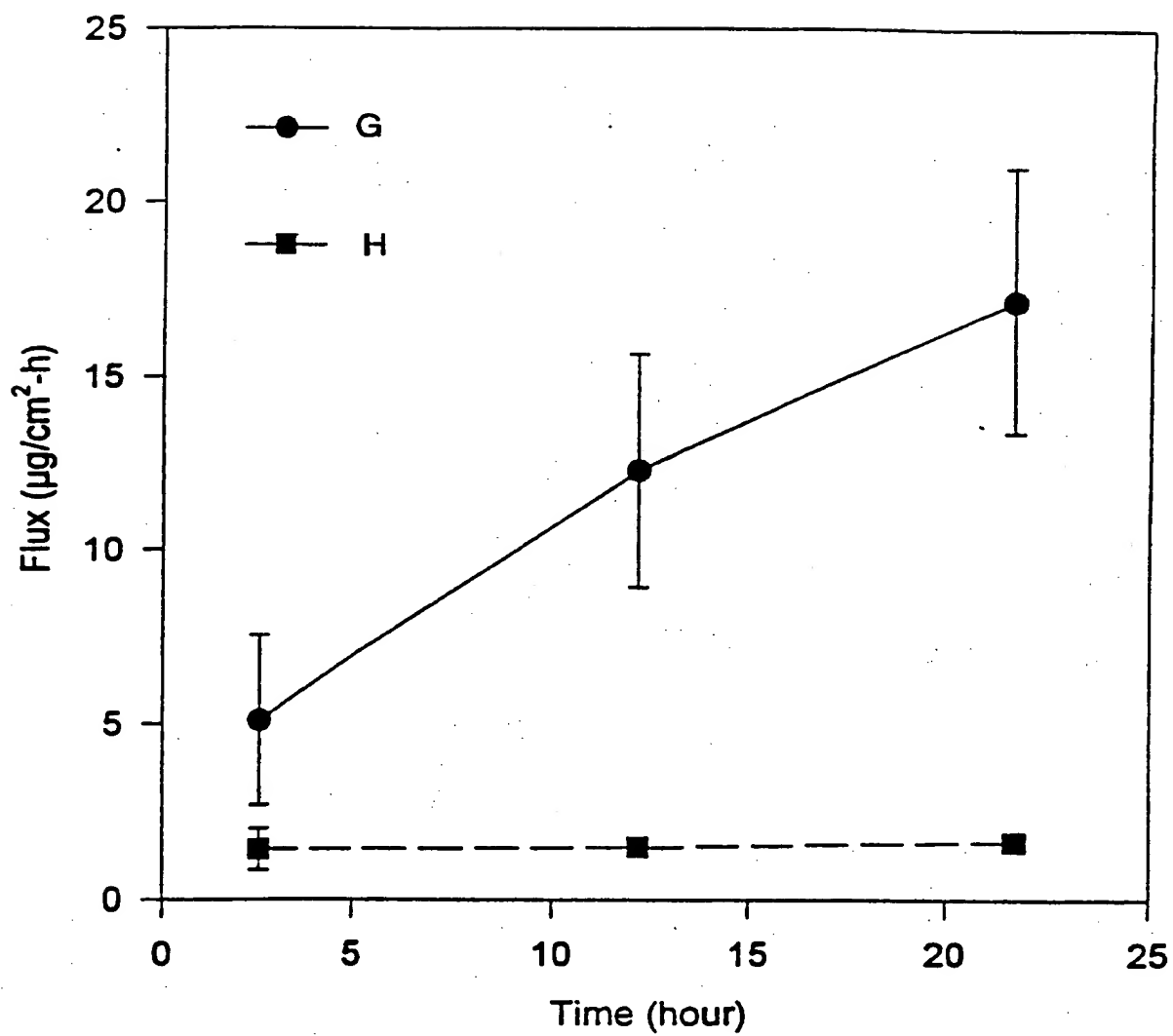


FIG. 16

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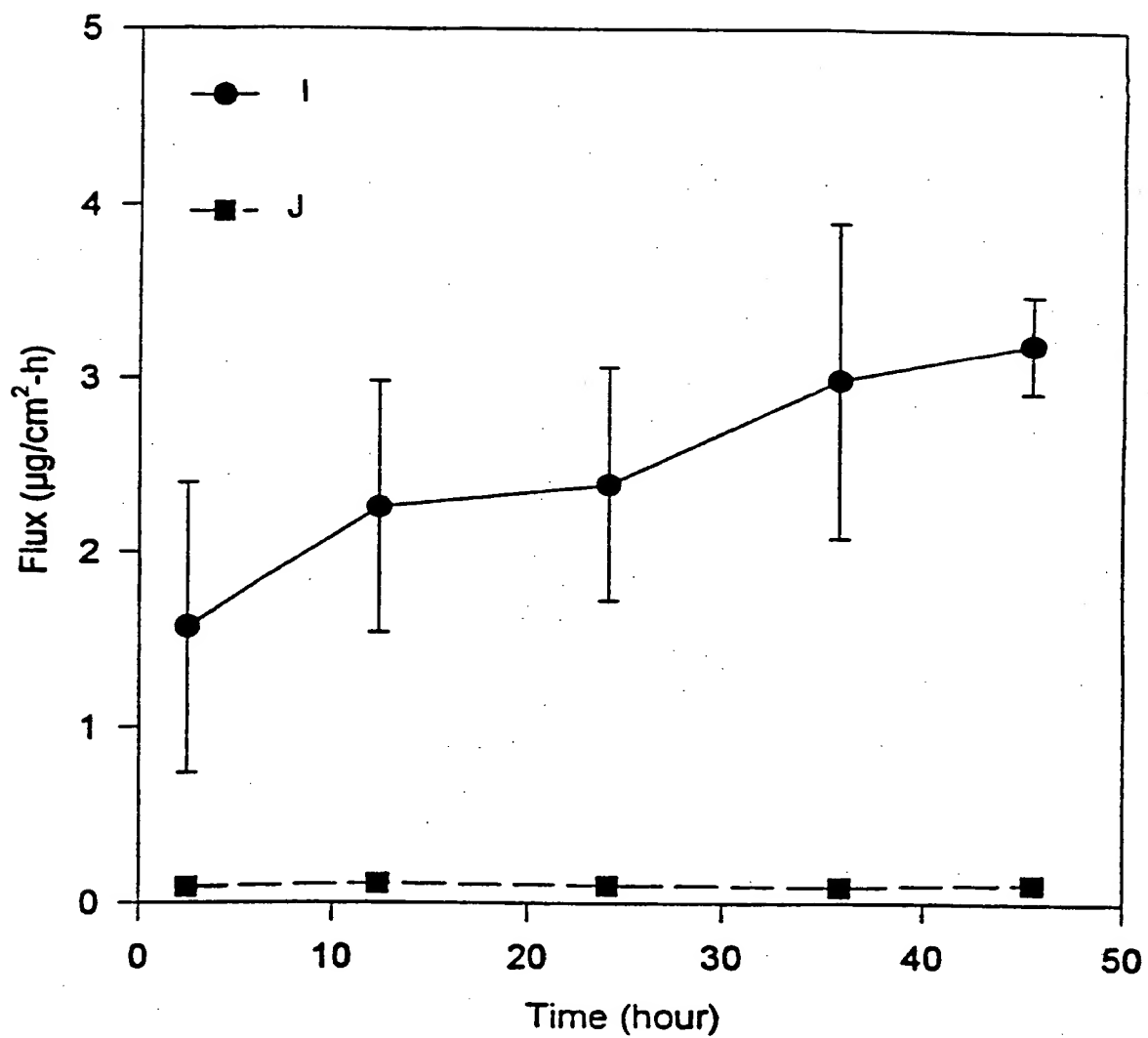


FIG. 17

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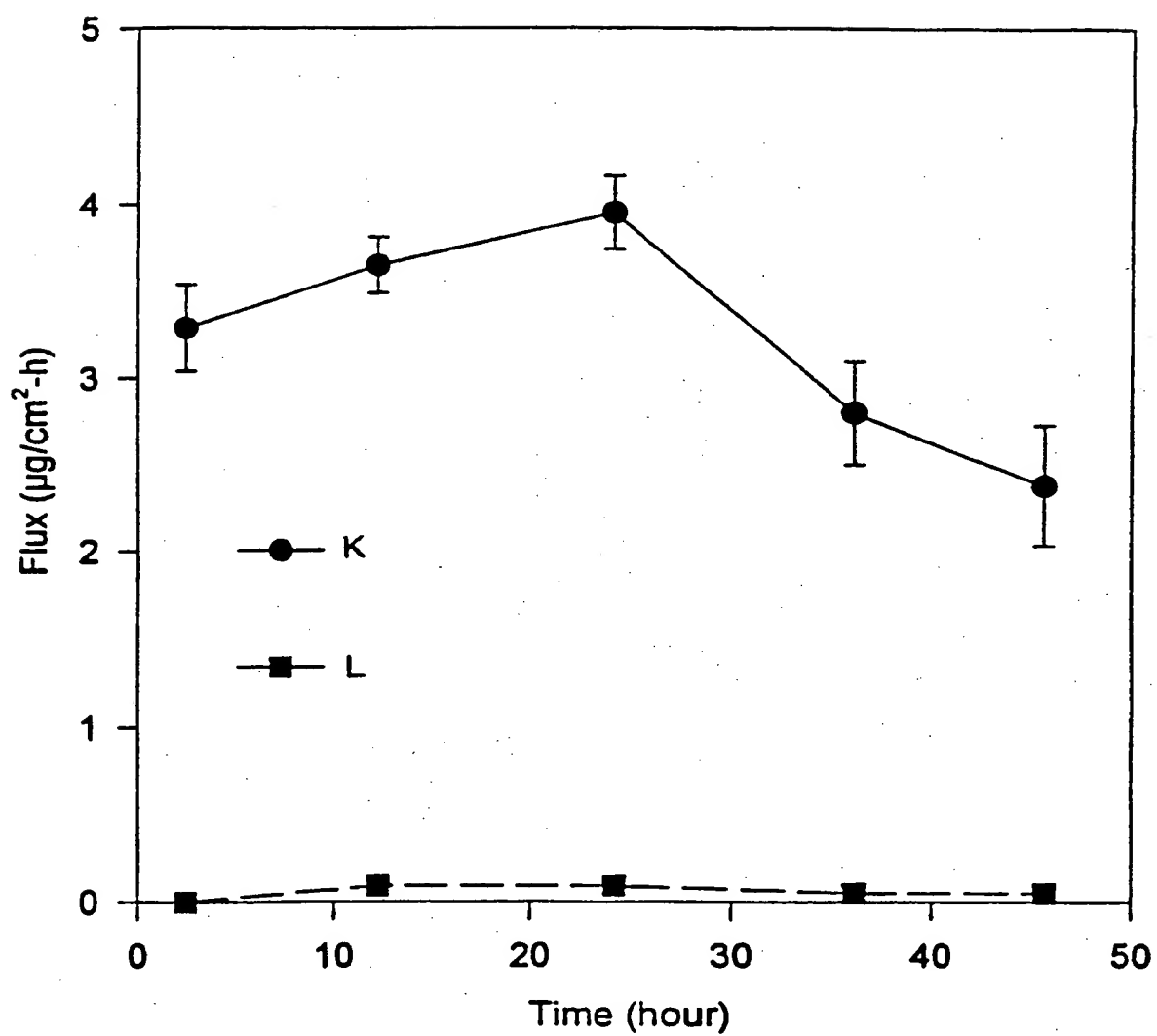


FIG. 18

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INTERNATIONAL SEARCH REPORT

Inter. Application No

PCT/US 97/18956

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/70 A61K47/10 A61K47/12 A61K47/14

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 96 40139 A (ALZA CORP ; YUM SU II (US); NELSON MELINDA K (US); CAMPBELL PATRICI) 19 December 1996 see page 13, line 1 - line 10 see page 21, line 24 - page 22, line 13 see page 29 - page 31; example 6 ---	1-5, 12-18
X	WO 96 19976 A (PACIFIC CORP) 4 July 1996 see page 16, line 2 - line 18 see page 19 - page 21; tables 1,2 ---	1-4, 15-17, 29, 31, 32
X	WO 92 20378 A (LOHMANN THERAPIE SYST LTS) 26 November 1992 see page 5, line 22 - page 6, line 4 see page 10; example 3 see claim 3 ---	1-3, 15

-/--



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

23 April 1998

Date of mailing of the international search report

14/05/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040. Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>KADIR R. ET AL: "Penetration of theophylline and adenosine into excised human skin from binary and ternary vehicles: effect of a nonionic surfactant" J. OF PHARM. SCIENCES, vol. 78, no. 2, 1989, pages 149-153, XP002063173 see page 150; figure 1</p> <p>-----</p>	1-5

INTERNATIONAL SEARCH REPORT

information on patent family members

Inte 3 application No

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